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Antipsychotic drug-induced obesity in rats: correlation between leptin, insulin and body weight during sulpiride treatment

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Sulpiride (SUL, 20 mg kg^{-1} day^{-1}) induces weight gain, hyperphagia, hyperprolactinemia, hypogonadism, and perhaps increased insulin sensitivity in rats. Leptin seems to signal the brain about the size of body fat stores and nutrient metabolism. We evaluated the basal serum leptin levels in rats after acute (1 h) or prolonged SUL or vehicle administration (10, 20 and 30 days). At days 10 and 30 leptin was also assessed during a glucose overload test. As the maximal weight gain during SUL administration is observed at days 10–15 of treatment, leptin was measured in a comparison group of insulin-treated rats (5 IU day^{-1} for 10 days). SUL-treated rats significantly gained weight. However, leptin levels were not significantly increased at any time-point of treatment. SUL did not affect insulin levels either. By contrast, leptin levels were significantly elevated after insulin administration, along with weight gain and hyperinsulinemia. An opposite correlation was also observed at day 10: leptin and insulin correlated negatively in the SUL group and positively in the insulin group. In addition, leptin and the magnitude of weight gain tended to correlate positively after SUL treatment, but negatively after insulin administration. SUL-treated rats, thus, appear to exhibit an unusual type of weight gain, characterized by normal circulating leptin and insulin levels. Such a particular leptin profile may be related to hyperprolactinemia, hypogonadism or lack of hyperinsulinemia. *Molecular Psychiatry* (2000) **5,** 70–76.

Keywords: leptin; insulin; glucose; prolactin; weight gain; antipsychotic drugs; rats; sulpiride

Introduction

Excessive body weight gain is often observed during chronic administration of typical and atypical antipsychotic drugs (AP) in psychiatric patients. This side-effect impairs health and promotes premature abandonment of treatment.[1–5]

Prolonged administration of diverse AP also increases body weight in female rats.[6–17] During SUL treatment (a D_2–D_3 dopamine receptor antagonist[18]), the rats display hyperphagia,[6,13] hyperprolactinemia,[11–13] and disruption of the vaginal cycle suggesting drug-induced hypogonadism.[11–13,16] Contrary to most types of obesity in humans and rodents,[19–22] insulin resistance (defined as basal hyperinsulinemia, along with normo- or hyperglycemia) is not observed in SUL-treated rats.[13–15]

Leptin is synthesized and secreted from fat and muscle cells, and it appears to be a signal of the size of the adipose mass, glucose and lipid metabolism. Thus, leptin (and insulin) integrate the long-term homeostasis of fat stores.[19–22] Therefore, it is expected that circulating serum leptin and the expression of the leptin gene in adipose tissue are enhanced as long as body weight increases. Most obese mammals (including humans) have elevated leptin and insulin levels, and they appear to be resistant to leptin-induced anorexia.[19–22] Insulin increases the expression of the leptin gene in rodents[23] and in adipocytes *in vitro*.[24] In addition, a positive correlation between serum leptin and basal insulin levels, and a negative correlation between plasma leptin and insulin sensitivity have been demonstrated.[25] Therefore, the lack of hyperinsulinemia and insulin resistance observed in AP-treated rats[14,15] should modify leptin levels during AP-induced weight gain.

Leptin and the reproductive hormones also interact in a complex way. For instance, leptin reverses the congenital deficiencies in pituitary hormones and the morphological anomalies in the uterus, ovaries and testis of obese *ob/ob* mice.[26] In addition, in the wild-type female mice, leptin accelerates the maturation of the reproductive tract,[27] and a surge in plasma leptin concentration is observed in prepubertal boys.[28] These findings suggest that the imbalance of reproductive hormone observed in AP-treated rats should also affect leptin levels.

Recently Bromel *et al*[29] and Kraus *et al*[30] reported an increase in leptin levels and body weight gain in psychiatric patients treated with clozapine and olanza-

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pine. Nevertheless, a relation between AP-induced weight gain and leptin in rats has not yet been reported.

In the present report we evaluated the serum levels of leptin and correlated them with body weight gain, insulin and glucose in basal conditions, and during a glucose tolerance test after administration of the AP sulpiride in rats.

Methods

Animals
Adult female rats of the Wistar strain weighing between 200–220 g were individually (acute and 20-day SUL administration) or two per cage (10- and 30-day SUL administration) housed under a 12:12 light-dark schedule, with light on at 7:00. Water and a high fat diet (66.6% powdered Purina chow pellets and 33% corn oil) were available *ad libitum*. Body weight gain (BWG) and food intake (FI) were recorded daily to the nearest 0.1 g. Care of animals followed the guide lines of the Institute of Laboratory Animal Resources.[31]

Drug treatment
Racemic sulpiride (Sigma, St Louis, MO, USA; 20 mg kg^{-1} i.p.) or vehicle i.p. (0.1 N HCl with pH adjusted to 7 with 0.1 N NaOH) were administered daily at 15:00 h. Blood samples were obtained 1 h after acute drug administration, and after 10, 20 and 30 days of treatment. Serum was kept at −70°C until hormone and glucose assays.

Procedure
Each experiment and every time-point of the glucose tolerance test was conducted in different animals. For the acute and 20-day studies, 10 rats received either SUL or VEH. Blood was obtained by decapitation from the trunk vessels. The basal levels of glucose, insulin and leptin were then determined. In the 10- and 30-day experiments, 72 rats were divided into two groups of 36 subjects each, and received daily doses of either SUL or VEH i.p. These rats were deprived of food for 8 h, and were decapitated at 7:00 h in order to obtain blood samples for both basal and after a glucose overload (2 g kg^{-1} i.p.) measurements. Basal prolactin levels were only assessed after 30 days of treatment.

Previous experiments have shown that the maximal BWG during SUL administration is observed at days 10–15 of treatment.[6–15] Therefore, we compared the leptin levels after 10 days of SUL treatment with those obtained after insulin-induced BWG in 16 animals receiving daily injections of insulin (Lilly, Mexico, DF; 5 IU s.c. for 10 days).

Serum glucose (mg dl^{-1}) was assessed by an enzymatic method from Boehringer (Mannheim, Germany); insulin (mIU ml^{-1}) and prolactin (ng ml^{-1}) were determined by radioimmunoassay with kits for measuring those hormones in rats (INCSTAR Corp, Minnesota, USA). Kits for the assessment of leptin in rats (ng ml^{-1}) were obtained from Lipco, MO, USA. The intra-assay variation was less than 10% in all the experiments.

Statistical analysis
BWG and FI were analyzed by a one-way ANOVA followed by Fisher least-significant difference test, by two-way ANOVA and by two-tailed *t*-test for unrelated samples. Leptin and insulin levels did not follow a normal distribution, therefore, simple and multivariate linear correlation analyses were conducted after logarithmic transformation of the data. Multiple regression analysis was conducted taking BWG as the dependent variable, and leptin, insulin and glucose levels as the independent variables. Comparisons between the treatment groups were carried out with the non-parametric procedures of Mann–Whitney U test (two groups) and Kruskall–Wallis H test (multiple groups). Prolactin serum levels were analyzed by the two-tailed *t*-test. Results were considered significant at the $P \leq 0.05$ level.

Results

Acute sulpiride administration
A single dose of SUL ($n = 10$) or VEH ($n = 10$) did not induce significant changes in the serum levels of leptin, insulin or glucose (Table 1); leptin: $U = 39.5$, $z = 0.8$, $P = 0.27$; insulin: $U = 49$, $z = 0.07$, $P = 0.93$; glucose: $U = 49$, $z = 0.07$, $P = 0.9$.

Long-term sulpiride administration

10-day sulpiride administration Both SUL and insulin significantly increased BWG (g): SUL group, 16.7 ± 1.1; VEH group, 1.03 ± 1.06; insulin group, 53 ± 2.1: $f(2,70)$ 10.2, $P = 0.0001$. Fl was also significantly increased by SUL or insulin: mean daily food intake of every two rats (g): SUL group: 25.9 ± 0.28; VEH group: 22.6 ± 0.33; insulin group: 37.1 ± 0.84; treatment effect: $f(2,351) = 337$, $P = 0.0001$; time effect: $f(9,351) = 6.8$, $P = 0.0001$.

The leptin serum levels did not differ in the SUL or VEH group, either in basal conditions or after the glucose overload (Table 2): basal sample, $U = 36$, $z = 0.3$, $P = 0.69$; 60-min sample, $U = 30.5$, $z = 0.5$, $P = 0.5$; 90-min sample, $U = 19$, $z = 0.2$, $P = 0.5$. However, the basal

Table 1 Basal serum levels of leptin, insulin and glucose after acute sulpiride or vehicle administration

Treatment	*Leptin (ng ml^{-1})*	*Insulin (mIU ml^{-1})*	*Glucose (mg dl^{-1})*
Sulpiride $n = 10$	0.76 ± 0.5	47.6 ± 2.4	152 ± 4.9
Vehicle $n = 10$	1.5 ± 0.7	46.3 ± 2.6	153 ± 3.5
P	ns	ns	ns

Values represent mean ± SEM. ns = non-significant differences, Mann–Whitney U test (see text for statistics).

Table 2 Serum levels of leptin, insulin and glucose in basal conditions and following a glucose overload after 10 days of sulpiride, vehicle or insulin administration

Treatment		*Basal (n = 9)*	*30 min (n = 9)*	*60 min (n = 9)*	*90 min (n = 9)*
Sulpiride	Leptin	3.1 ± 1.6	–	2.8 ± 1	2.5 ± 1.8
Vehicle	Leptin	1.5 ± 0.9	–	2.8 ± 1	3.6 ± 1.5
Insulin	Leptin	29.1 ± 5.4*	–	–	–
P		0.0001		ns	ns
Sulpiride	Insulin	13.7 ± 1.4	19.5 ± 1.6	17.4 ± 4.1	14.1 ± 2.5
Vehicle	Insulin	10.7 ± 1.5	18.3 ± 1.9	13.8 ± 1.7	15.2 ± 2.4
Insulin	Insulin	254.1 ± 55*	–	–	–
P		0.0001	ns	ns	ns
Sulpiride	Glucose	107 ± 6.1	158 ± 11.8	161 ± 6.5	167 ± 10.5
Vehicle	Glucose	110 ± 10.1	171 ± 8.2	156 ± 8.1	148 ± 6.9
Insulin	Glucose	59 ± 3.3*	–	–	–
P		0.0001	ns	ns	ns

Values represent mean ± SEM. Leptin is expressed as ng ml^{-1}, insulin as mIU ml^{-1} and glucose as mg dl^{-1}. ns = non-significant differences between groups in the specific time point. (*) = significantly different in the insulin group, Kruskall–Wallis test (see text for statistics). The insulin group comprised 16 subjects.

leptin levels in the insulin-treated rats were significantly higher than those observed after SUL or VEH (Table 2): H (2) = 20.5, $P = 0.0001$.

As regards insulin levels, significant differences were observed between the SUL and VEH group neither in any of the time-points of the glucose tolerance test ($f(7,71) = 1.6$, $P = 0.1$) nor in the area under the insulin curve (SUL area: 29.8 ± 2.9; VEH area: 25.9 ± 1.6, $t(16) = 1.13$, $P = 0.27$). Obviously in basal conditions the insulin serum levels were considerably higher in the insulin-treated rats (Table 2): $H(2) = 25.2$, $P = 0.0001$.

With reference to the glucose levels, significant differences were observed *within* the groups along the diverse time-points of the glucose overload test: $f(7,71) = 8.2$, $P = 0.0001$. However, there were no significant differences *between* the SUL and VEH group in each time-point and in the area under the curve: SUL area: 268 ± 7.9; VEH area: 268 ± 7.3, $t(16) = 0.01$, $P = 0.98$. In basal conditions the glucose serum levels were significantly lower in the insulin-treated rats (Table 2): $H(2) = 23.2$, $P = 0.0001$.

20-day sulpiride administration Body weight gain was significantly higher in the SUL-treated rats: mean BWG (g): SUL group: 32.8 ± 3.1; VEH group: 4.8 ± 2.1, $t(18) = 7$, $P = 0.0001$. Food intake was also significantly increased by SUL: mean daily food intake (g) = SUL group: 12.9 ± 0.6; VEH group: 10.7 ± 0.2; treatment effect: $f(1,36) = 14.7$, $P = 0.0005$; time effect: $f(2,36) = 8.2$, $P = 0.001$. No significant differences between the SUL and VEH groups were observed in the basal serum levels of leptin, insulin or glucose (Table 3): for leptin, $U = 26.5$, $z = 1.2$, $P = 0.22$; for insulin, $U = 39$, $z = 0.08$, $P = 0.92$; for glucose, $U = 38$, $z = 0.17$, $P = 0.85$.

30-day sulpiride administration BWG (g) was significantly larger in the SUL group: 42.0 ± 2.5; VEH group: 24.0 ± 5.2, $t(70) = 5.2$, $P = 0.0001$. Food intake was also significantly increased by SUL: mean daily food intake of every two rats: SUL group: 23.7 ± 0.2; VEH group: 22.9 ± 0.1; $f(1,1040) = 11.9$, $P = 0.0006$.

Table 3 Basal serum levels of leptin, insulin and glucose after 20 days of sulpiride or vehicle administration

Treatment	*Leptin (ng ml^{-1})*	*Insulin (mIU ml^{-1})*	*Glucose (mg dl^{-1})*
Sulpiride $n = 10$	1.4 ± 0.6	13.4 ± 4.7	97.6 ± 5.6
Vehicle $n = 10$	0.7 ± 0.6	14.8 ± 5.5	99.4 ± 8.6
P	ns	ns	ns

Values represent mean ± SEM. ns = non-significant differences, Mann–Whitney U test (see text for statistics).

The leptin serum levels did not differ between the SUL and VEH group, either in basal conditions or after the glucose overload (Table 4): basal sample, $U = 39$, $z = 0.1$, $P = 0.9$; 60-min sample, $U = 29$, $z = 1$, $P = 0.3$; 90-min sample, $U = 27$, $z = 0.4$, $P = 0.63$.

As regards the insulin levels, even though significant differences were observed within the groups, no significant differences were observed *between* them when comparisons were carried out in specific time-points of the glucose overload test: $f(7,71) = 10.2$, $P = 0.0001$ (Table 4). The area under the insulin curve did not differ between the SUL and VEH groups either: SUL area: 75.3 ± 1.8; VEH area: 76.7 ± 3.1, $t(16) = 0.4$, $P = 0.69$.

With reference to the glucose levels, significant differences were observed *within* the groups along the diverse time-points of the glucose overload test: $f(7,71) = 25.3$, $P = 0.0001$. In addition, after 60 min of the glucose overload, the glucose levels were significantly lower in the SUL group: $U = 9$, $z = 3.7$, $P = 0.0002$. The area under the glucose curve was also

Table 4 Serum levels of leptin, insulin and glucose in basal conditions and following a glucose overload after 30 days of sulpiride or vehicle administration

Treatment		*Basal (n = 9)*	*30 min (n = 9)*	*60 min (n = 9)*	*90 min (n = 9)*
Sulpiride	Leptin	0.15 ± 0.8	–	2.8 ± 1	2.5 ± 1.8
Vehicle	Leptin	0.20 ± 0.1	–	2.8 ± 1	3.6 ± 1.5
P		ns		ns	ns
Sulpiride	Insulin	18.2 ± 6.1	53.1 ± 1.2	46.8 ± 1.2	36.5 ± 5.7
Vehicle	Insulin	22.7 ± 6.7	48.9 ± 3.7	48.9 ± 3.4	44.5 ± 2.2
P		ns	ns	ns	ns
Sulpiride	Glucose	84.5 ± 3.4	185 ± 9.1	163 ± 12	137 ± 9.2
Vehicle	Glucose	110 ± 6.7	257 ± 11	177 ± 17	163 ± 6.1
P		ns	0.05	ns	ns

Values represent mean ± SEM. Leptin is expressed as ng ml^{-1} insulin as mIU ml^{-1} and glucose as mg dl^{-1}. ns = non-significant differences between groups in the specific time point, Mann–Whitney U test. The area under the glucose curve was significantly lower in the SUL group (see text for statistics).

significantly lower in the SUL group: 276.6 ± 11.2; VEH group: 322 ± 13.6, $t(16) = 2.64$, $P = 0.017$.

Serum prolactin levels were significantly increased by SUL: 55.6 ± 1.1; VEH group: 24.8 ± 6.8, $t(18) = 4.4$, $P = 0.0004$.

Simple correlation analysis

Table 5 depicts the correlation coefficients obtained in the SUL and VEH groups. Significant correlation was observed between leptin and insulin in the SUL group: it was a negative correlation at day 10 (Figure 1), and a positive one at day 20 of treatment. In this group, after acute SUL administration, a positive correlation was found between insulin and glucose. In addition, a trend toward a positive correlation ($P = 0.08$) between the magnitude of BWG and leptin levels was observed at day 10.

Body weight gain and glucose levels correlated significantly; such a correlation was positive in the SUL group and negative in the VEH group. No significant correlation was observed in any treatment group between the prolactin levels and body weight gain, leptin, insulin or glucose serum levels (data not shown).

Table 6 shows the correlation coefficients observed in the subjects treated with insulin for 10 days. The magnitude of weight gain correlated negatively with all the serum variables; the correlation was significant with insulin and glucose, and it reached marginal significance with leptin ($P = 0.07$). In addition, significant positive correlation was observed between leptin and insulin (Figure 1), and between insulin and glucose.

Multivariate regression analysis

The composite interaction of leptin, insulin and glucose did not significantly predict BWG after SUL or VEH administration: for day 10: SUL, $r = 0.62$, $P = 0.4$; VEH, $r = 0.8$, $P = 0.12$; for day 20: SUL, $r = 0.56$, $P = 0.4$; VEH, $r = 0.41$, $P = 0.8$; for day 30: SUL, $r = 0.79$, $P = 0.14$. In the VEH group, the glucose coefficient displayed a marginal significance: $r = 0.85$, $f(3,8) = 4.5$, $P = 0.06$, β coefficient = –0.6, $t = 3.3$, $P = 0.019$.

In the insulin-treated rats, only insulin levels significantly predicted BWG: $r = 0.78$, $f(3,15) = 6.4$, $P = 0.007$; β coefficient = –0.016, $t = 2.4$, $P = 0.02$.

Table 5 Correlation coefficients between body weight gain, and basal levels of leptin, glucose and insulin during acute or prolonged sulpiride or vehicle administration

	Treatment	*Acute*	*10 days*	*20 days*	*30 days*
Leptin *vs* insulin	SUL	0.26	–0.73[a]	0.63[a]	–0.28
	VEH	0.11	0.36	–0.12	0.43
Leptin *vs* glucose	SUL	–0.33	0.43	–0.51	–0.23
	VEH	0.15	–0.14	0.23	0.14
Insulin *vs* glucose	SUL	0.65[a]	–0.3	–0.50	0.02
	VEH	–0.56	–0.02	–0.58	0.20
BWG *vs* leptin	SUL	–	0.61[b]	0.40	0.58
	VEH	–	0.41	–0.27	0.26
BWG *vs* insulin	SUL	–	–0.32	0.09	–0.09
	VEH	–	–0.25	0.03	–0.06
BWG *vs* glucose	SUL	–	0.30	0.40	0.67[a]
	VEH	–	–0.70[a]	0.06	–0.76[a]

[a]$P < 0.05$; [b]$P = 0.08$.

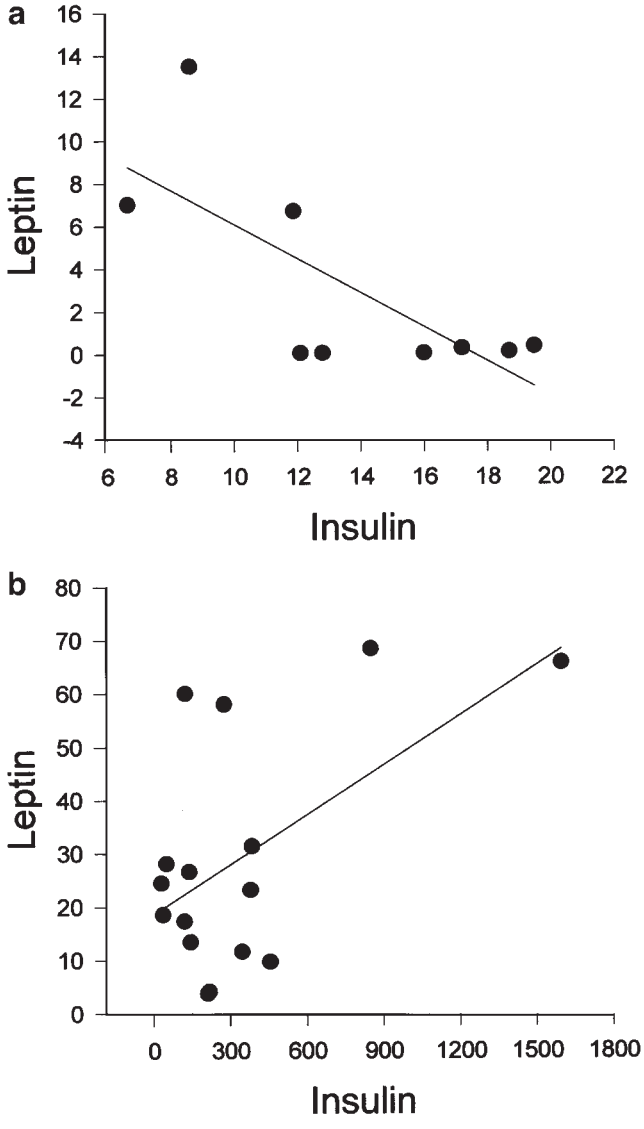

Figure 1 Correlation between the serum levels of leptin and insulin after 10 days of treatment with (a) sulpiride (20 mg kg^{-1}) or (b) insulin (5 IU). Leptin and insulin correlated negatively after sulpiride administration: $r = -0.73$, $f(1,9) = 8.1$, $P = 0.024$. In the insulin group it was a positive correlation: $r = 0.56$, $f(1, 15) = 6.4$, $P = 0.023$.

Table 6 Correlation between body weight gain, basal serum levels of leptin, insulin and glucose after administration of insulin for 10 days

	Leptin	*Insulin*	*Glucose*
Weight gain	–0.46[b]	–0.78[a]	–0.59[a]
Leptin	–	0.56[a]	0.35
Insulin	–	–	0.75[a]
Glucose	–	–	–

[a]$P < 0.05$; [b]$P = 0.07$.

Discussion

As previously reported, SUL treatment induced significant BWG, mild hyperphagia, and hyperprolactinemia.[6–16] However, the leptin serum levels were similar in the SUL and VEH group after either acute or prolonged treatments. By contrast, 10-day insulin administration induced a significant increase in leptin levels, along with BWG and hyperphagia.

The insulin serum levels, either in basal conditions or after a glucose overload were not significantly affected by SUL. Glucose serum levels and the area under the glucose curve were similar in the SUL and VEH after acute, 10-day and 20-day treatments. However, after 30 days of SUL administration, the area under the glucose curve significantly decreased. As discussed elsewhere,[14,15] the glucose and insulin response in SUL-treated rats shows that the BWG is not associated with hyperinsulinemia and insulin resistance. By contrast, it has been speculated that an increased insulin sensitivity may be involved in the obesity induced by this antipsychotic drug in rats.[14,15]

It is unclear at present why the leptin levels remained unchanged during SUL administration, even though the animals displayed significant BWG. Bromel *et al*[29] and Kraus *et al*[30] reported that BWG induced by clozapine or olanzapine was associated with an increase in leptin levels in psychiatric patients. The disparate results might be due to drug (sulpiride *vs* clozapine or olanzapine) or species (rats *vs* humans) differences. Friedman and Halaas[20] proposed that normal leptin level obesity, which is observed in 5–10% of humans with primary obesity, reflects a decreased leptin expression per adipocyte. However, no evidence is available to suspect a direct interaction between D_2–D_3 brain dopamine receptor blockade and the synthesis, release, transport and catabolism of leptin. Since insulin increases the expression of the leptin gene in rodents[23] and in adipocytes *in vitro*,[24] the absence of hyperinsulinemia in SUL-treated rats may prevent an increase in leptin levels. However, leptin displays a better correlation with glucose utilization by the adipocytes than with insulin levels *in vitro*.[32] SUL-treated rats display normo- or a trend to hypoglycemia,[13–15] which suggests an adequate or enhanced uptake of glucose by the peripheral tissues. Therefore, if glucose utilization were normal, there would be no reason to see leptin level enhancement in SUL-treated rats. Hence, other factors must be investigated. For instance, leptin levels are also notably influenced by glucocorticoids, catecholamines, glucosamine[33] and lypolisis products,[21] and the condition of these variables in SUL-treated animals has not been examined.

SUL induces abnormal vaginal cycles, and a strong hyperprolactinemia which impairs the synthesis of gonadal steroids.[11–13,16,34] It is tempting to speculate that the relative hypogonadic status observed during SUL treatment, in some way promotes low leptin levels, as observed in normal prepubertal humans[28] and genetically infertile mice.[26]

Finally it could be argued that leptin did not increase

because the weight gain during SUL administration is rather modest. The final body weight after 30 days of SUL treatment was 10% higher than in VEH-treated rats. By contrast, body weight in insulin-treated rats was 20% above their controls. This explanation seems unlikely, because leptin levels are sensitive to small changes in body weight. In fact, we have found that healthy men receiving SUL for 1 month displayed a significant increase in leptin levels, along with a small (but significant) weight gain of 0.6 kg as an average (unpublished observations).

A significant negative correlation between leptin and insulin was found after 10 days of SUL administration. This result resembles the negative correlation that has been reported between serum leptin and insulin sensitivity in humans and rodents.[19,20,22,26] In fact, it is around day 10 that increased insulin sensitivity and maximal weight gain during SUL administration has been observed.[14] Interestingly enough, in rats receiving insulin for 10 days, leptin and insulin also correlated significantly but in a positive way, suggesting profound biological differences between the SUL and the insulin models of obesity.[9] However, at day 20 of SUL treatment, leptin and insulin levels correlated positively, which seems to be the most common relationship between those hormones in hyperinsulinemic obese subjects. This appears to be a contradictory result, because even under prolonged SUL administration (30 days in this experiment), the insulin and glucose response to a glucose overload points to increased insulin sensitivity, instead of insulin resistance and hyperinsulinemia. Collectively these results suggest that insulin sensitivity in SUL-treated rats is differentially expressed at diverse time-points of treatment. The clarification of this important point requires the direct assessment of insulin sensitivity.

The correlation analysis between body weight gain and basal serum glucose levels also produced contradictory results. A significant positive correlation was found at day 30 of SUL administration, whereas during VEH treatment it was a negative one. At this point of treatment, the area under the glucose curve was significantly lower in the SUL group than in the VEH group, suggesting increased insulin sensitivity in SUL-treated animals.

In conclusion, we report here that female rats under acute or prolonged administration of the antipsychotic drug SUL display persistent normal serum leptin levels, in spite of a significant body weight gain after long-term treatment. It is unknown by this time if the same endocrine profile is observed after administration of antipsychotic drugs with different pharmacological features from that of SUL. In any event, normal leptin levels, along with the absence of basal hyperinsulinemia hint profound differences between this animal model of drug-induced weight gain and most types of obesity in humans and rodents.[19–22]

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